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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,938	04/05/2004	Baiyang Wang	1861.1670002/JUK/AWL	3825

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,938	WANG, BAIYANG	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-81* is/are pending in the application.

4a) Of the above claim(s) *1-28,35-77 and 81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-34 and 78-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response received February 7, 2007 is acknowledged.

Claims 1-81 are pending in the instant application.

Applicant's election with traverse of Group III, claims 29-34 and 78-80 as they read on methods of treating cancer by administering antibodies that bind tissue factor, and the species of non-small cell lung cancer in the reply filed on February 7, 2007 is acknowledged. The traversal is on the grounds that a three-way restriction between products, processes of making products and the methods of using products cannot be made unless the product is distinct from the method of its manufacture as per 37 CFR 1.141(b), and that there is no undue burden in searching groups I, III, VII, and VIII simultaneously.

These arguments have not been found persuasive because the instant claimed products, antibodies that bind tissue factor but do not inhibit its activity, can be made by a variety of methods. Such methods include the use of antibody phage display libraries, standard hybridoma technology (Group IV), and expressing antibodies of defined amino acid sequence recombinantly (Group VI). MPEP 806.05(f) states that distinctness between products and methods of making said products can be shown if the products can be made by distinct methods, and as explained above and in the restriction requirement mailed January 10, 2007 the claimed products can be made by many distinct methods.

Applicant also argues that there is no search burden. This argument is not persuasive because as was stated in the restriction requirement, the classifications of the instant claimed inventions and the literature searches required were distinct and non-coextensive. Further, applicant has not stated on the record or provided an evidentiary reference that finding art which anticipates or renders obvious the invention of one group would also anticipate or render obvious the invention of the other groups.

In view of the prior art, the species election has been extended to encompass breast, colon and prostate cancer in addition to the elected species of non-small cell lung cancer.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-28, 35-77, and 81 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on February 7, 2007.

Information Disclosure Statement

3. Applicant's IDS forms received 11/9/04, 3/23/05, and 6/7/05 are acknowledged and have been considered. Reference AR23 on the 3/23/05 IDS, Abdulkadir et al., has been considered but has been lined through as being a duplicate of reference AT10 on the 11/9/04 IDS.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 29, 30, 32, 33, 78, and 79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of diagnosing non-small cell lung, breast, colon and prostate cancer by administering antibodies that bind tissue factor but do not inhibit tissue factor mediated coagulation, and being enabling for methods of treating lung and breast cancer by administering said antibodies, does not reasonably provide enablement for methods of treating or diagnosing the genus of all cancers using said antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant has claimed methods of using antibodies that bind tissue factor to diagnose and treat human cancers. The antibodies used in applicant's methods comprise the ability to bind tissue factor without inhibiting the ability of tissue factor to mediate blood coagulation. The specification does not disclose a working example wherein said anti-tissue factor antibodies were administered to treat cancer or disclose an example wherein said antibodies were used in diagnostic methods that identified cancer patients.

The prior art indicates that detection of tissue factor is diagnostic for many types of cancer, including breast, colon, prostate and non-small-cell lung cancer (Chen et al., Vrana et al., Seto et al. (of record as reference AT7), Abdulkadir et al. (of record as reference AT10), Akashi et al. (of record as reference AS11), Ohta et al. (of record as reference AR19), Koomagi et al. (of record as reference AS5), and Sawada et al. (of record as reference AS7), see entire documents). Further, administration of antibodies that bind tissue factor appears to provide clinical benefit in the treatment of breast and lung cancers (Ngo et al., see entire document particularly the abstract, and Edgington et al., US Patent 5,223,427, of record as reference AB1, see particularly lines 3-11 of column 23). However, Callander et al. undertook a survey of solid tumors and found that some tumor types consistently failed to stain positively for tissue factor expression (of record as reference AS1, see entire document, particularly the bottom left column of page 1196 and Table 1). Further, Kageshita et al. have reported that tissue factor was equally expressed in benign and malignant melanocytic lesions (see entire document, particularly the abstract and the sentence spanning the left and right columns of page 198). Therefore, it does not appear reasonable that detection of tissue factor expression can be used as a generic marker for all types of cancer.

The methods claimed by applicant are limited in that they comprise administration of antibodies that bind tissue factor with the special property that the administered antibody does not inhibit tissue factor mediated blood coagulation as compared to a normal plasma control. Most of the antibodies known in the prior art that bind tissue factor have the property of inhibiting coagulation (Soule et al., US patent 5,506,134,of record as reference AD1 and Wong et al., US patent 5,986,065, of record

as reference AG1, see entire documents). Inhibition as compared to a normal plasma control is defined in paragraph 127 wherein it is disclosed that such a "non-inhibitory" antibody will exhibit a clotting time of not more than 150% of the control when performed in the well known, art recognized, two stage prothrombin assay as is disclosed paragraph 204 of the instant specification and in Morrissey et al. (of record as reference AR6, see entire document, particularly pages 250 and 251).

Edgington et al. teach that non-inhibitory antibodies that bind tissue factor are to be used in treating lung and breast cancer (see particularly lines 3-11 of column 23). Ruf et al. (WO 94/05328, of record as reference AM1) administered both inhibitory and non-inhibitory antibodies that bind tissue factor in a mouse model of metastaic melanoma. Ruf et al. observed that antibodies which inhibited the coagulation activity of tissue factor reduced melanoma metastasis whereas antibodies which did not inhibit tissue factor coagulation activity were not therapeutically effective (see entire document, particularly Example V beginning on page 53, most particularly Table 2 and the paragraph spanning pages 55 and 56). As such, it does not appear that administering antibodies that fail to inhibit tissue factor mediated blood coagulation would predictably treat the genus of all cancers. Further note that paragraph 151 of the specification indicates that melanoma is a solid tumor.

Claims 29-34 all ultimately refer back to claim 1, which recites an antibody which does not inhibit tissue factor mediated blood coagulation and is capable of initiating an Fc-mediated mechanism. Applicant provides guidance concerning the meaning of "Fc-mediated mechanism" in paragraph 137 that discloses that this term refers to the initiation of an immune response to antigens mediated through Fc receptor activation. The specification further discloses that Fc-mediated mechanisms include antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). The specification discloses that multiple antibodies were generated which bind tissue factor and do not inhibit its ability to mediate coagulation (paragraph 204) and that such antibodies comprise ADCC activity (paragraph 205).

It is know in the art that the effector function of an antibody is strongly influenced by the Fc domain present in the antibody, and that this property can be determined by

selection of an appropriate Fc region for the antibody (Presta, see entire document). For example, if increased ADCC were desired in a particular human therapeutic setting, a skilled artisan would know that the therapeutically administered antibody should comprise a human IgG1 Fc domain (Ibid., see particularly the top left paragraph of page 243). However, it is also known that anti-cancer antibodies can work via many mechanistic pathways, often simultaneously. For example, a therapeutic antibody can initiate apoptosis in the tumor cell upon crosslinking of the target antigen, allow for complement fixation and lysis based upon antigen binding, allow for phagocytosis, and/or allow for ADCC (Ibid., see particularly pages 240-246). It is also known that cytotoxic agents can be directly attached to antibodies to kill tumor cells (ibid., see particularly the left column of page 248). All of these diverse activities are predicated upon the binding of the antibody to its target antigen, in the instant case tissue factor. As has been discussed above, tissue factor is not expressed in many different types of cancer. Since tissue factor is not expressed on all cancers, an antibody that binds tissue factor cannot reasonably be used to treat all cancers. Even when tissue factor is expressed, such as in melanoma, treatment with non-inhibitory antibodies that bind tissue factor did not effectively treat the cancer as was taught by Ruf et al. The specification does not appear to teach a mechanism or provide guidance concerning how to distinguish between cancers that are or are not amenable to treatment with non-inhibitory anti-tissue factor antibodies.

Therefore, based upon the teachings of the art, the amount of guidance and direction in the specification, the lack of a working example of treatment in the instant specification, the fact that tissue factor is not expressed in all cancers, the fact that a non-inhibitory antibody failed to treat metastatic melanoma, and the apparent inability to predict which cancers will or will not be amenable to treatment via applicant's recited method, a skilled artisan would be unable to practice the full breadth of the claimed invention without first conducting additional, unpredictable research.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 29-34 and 78-80 are rejected under 35 U.S.C. 102(b) as being anticipated by Edgington et al., US Patent 5,223,427 (of record as reference AB1, see entire document).

Edgington et al. teach numerous antibodies that bind tissue factor and their methods of use (see entire document, particularly the abstract). Two functionally distinct groups of antibodies that bind tissue factor are disclosed that differ from one another based upon their ability to neutralize tissue factor initiated coagulation (see particularly lines 18-41 of column 21). One particular antibody disclosed by Edgington et al. that does not inhibit tissue factor mediated blood coagulation is TF9-10H10 (see particularly lines 35-41 of column 21). Antibodies that do not inhibit tissue factor mediated coagulation are taught as being used in methods of treating breast and lung cancer when the antibodies are coupled to anti-tumor agents and administered as part of an anti-tumor therapeutic composition (see particularly lines 3-11 of column 23). Anti-tumor agents are disclosed as comprising radionuclides such as ^{131}I (see particularly lines 12-17 of column 23). Note that ^{131}I is a "cytotoxic agent" as per paragraph 102 of the instant specification and that breast and lung carcinomas are "solid tumors" as per paragraph 151 of the instant specification. The non-tissue factor inhibiting antibody TF9-10H10 is also disclosed for use in in vivo and in vitro methods of detecting expression of human tissue factor (see particularly from line 67 of column 3 to line 26 of column 4, lines 1-53 of column 26. The antibodies used in such methods can be detected through either secondary reagents or by directly coupling a detectable reagent to said antibodies (see particularly lines 20-64 of column 24). Note that TF9-10H10 is a whole murine antibody molecule and therefore it comprises an Fc domain that can participate in Fc-mediated mechanisms.

Therefore, the prior art anticipates the claimed invention.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 29, 31, 33, 34, 78, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edgington et al., US Patent 5,223,427 (of record as reference AB1 on the 11/9/04 IDS, see entire document) in view of Koomagi et al. (of record as reference AS5 on the 11/9/04 IDS, see entire document).

The teachings of Edgington et al. have been discussed supra. These teachings differ from the instant claimed invention in that while they teach the detection and treatment of lung carcinomas, they do not specifically teach non-small-cell lung carcinomas.

Koomagi et al. teach that they observed a significant association between the expression of tissue factor on tumor cells and the susceptibility of the tumor cells to chemotherapy (see entire document, particularly the abstract). They further teach that tissue factor expression has predictive value in estimating survival for patients with non-small-cell lung cancer (see particularly the last sentence of the abstract and the penultimate paragraph of page 21). Specifically, they observed tumors that express tissue factor were generally more susceptible to treatment with an anti-tumor agent, and that patients who had tissue factor positive tumors tended to have shorter survival times (see particularly the abstract, Figure 2, and Table IV).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the methods of Edgington et al. that comprise the use of non-inhibitory antibodies that bind tissue factor in order to treat non-

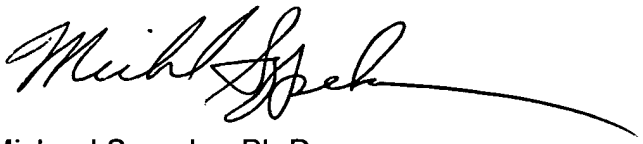
small-cell lung cancer. Motivation to do so comes from the teachings of Koomagi et al. that detection of tissue factor expression is of prognostic value in non-small-cell lung cancer and the teachings of Edgington et al. which set forth multiple ways by which tissue factor expression can be detected using non-inhibitory antibodies that bind tissue factor. A person of ordinary skill in the art would have been further motivated to treat patients with non-small-cell lung cancer using the treatment methods of Edgington et al. because Edgington et al. disclose that their treatment method is to be used to treat all lung carcinomas, a genus that comprises non-small-cell carcinoma, and because Koomagi et al. teach that tissue factor expressing tumors are more amenable to treatment with anti-tumor agents. As such, an anti-tissue factor antibody conjugated to a cytotoxic agent, such as those disclosed by Edgington et al., would be reasonably expected to bind tissue factor expressing non-small-cell lung cancer cells and kill said cells since such cells comprise an increased susceptibility to therapeutic agents as taught by Koomagi et al.

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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March 27, 2007